

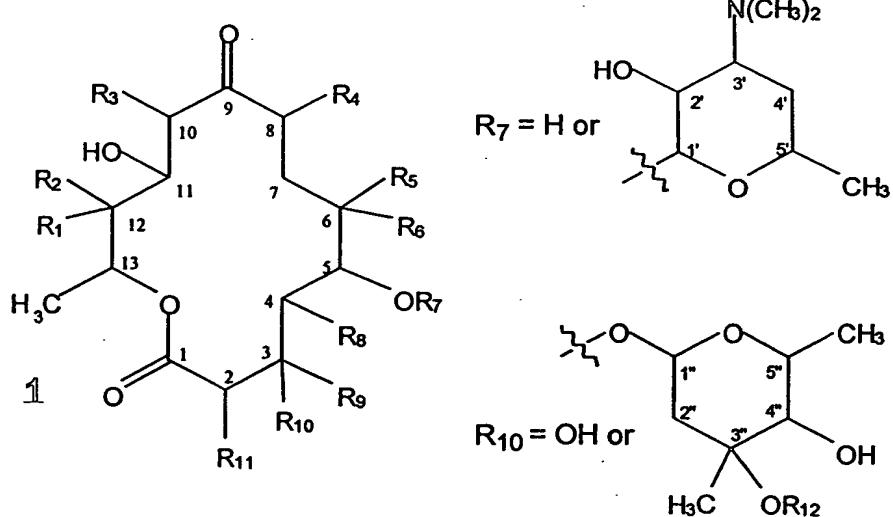
Claims

1. A 14-member macrolide which incorporates an acetate starter unit so that it has a 13-methyl substituent, with the proviso that it is not norerythromycin C, 6-deoxy-15-norerythromycin B or 6-deoxy-15-norerythromycin D.

2. 15-norerythromycin A.

10 3. 15-norerythromycin B.

4. A compound of the formula 1:



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or a pharmaceutically acceptable salt thereof, wherein:

R<sub>1</sub> is H or OH; R<sub>2</sub>-R<sub>4</sub> are each independently H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>5</sub> is H or OH; and R<sub>6</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>7</sub> is H or desosamine; R<sub>8</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>9</sub> is OH, mycarose (R<sub>12</sub> is H), or cladinose (R<sub>12</sub> is CH<sub>3</sub>), R<sub>10</sub> is H; or R<sub>9</sub> = R<sub>10</sub>

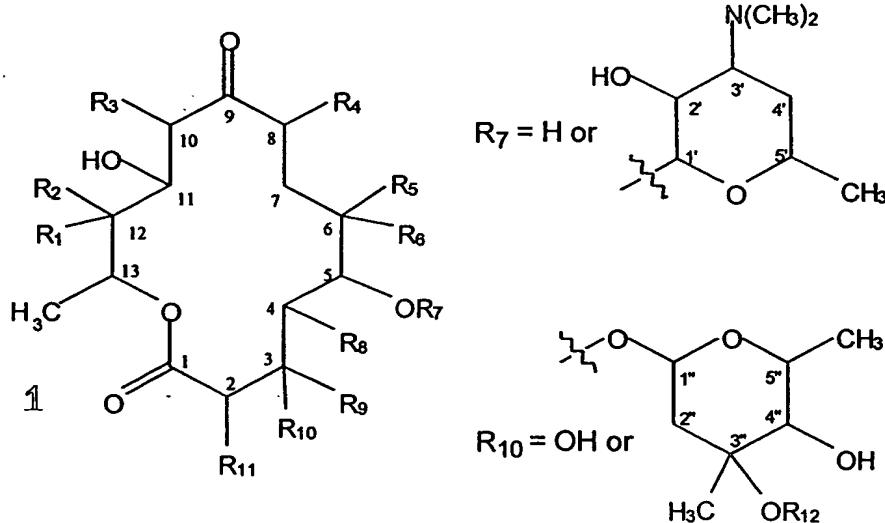
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= O; and R<sub>11</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>, with the proviso that when R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>, R<sub>6</sub> is CH<sub>3</sub>, R<sub>8</sub> is CH<sub>3</sub>, and R<sub>11</sub> is CH<sub>3</sub>, then R<sub>1</sub> and R<sub>5</sub> are not H and R<sub>12</sub> is not H; or also when R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>, R<sub>6</sub> is CH<sub>3</sub>, R<sub>8</sub> is CH<sub>3</sub>, and R<sub>11</sub> is CH<sub>3</sub>, then R<sub>1</sub> and R<sub>5</sub> are not OH and R<sub>12</sub> is not H.

5. A compound according to claim 4 wherein R<sub>1</sub> is OH; R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>; R<sub>5</sub> is OH; R<sub>6</sub> is CH<sub>3</sub>, R<sub>7</sub> is desosamine; R<sub>8</sub> is CH<sub>3</sub>; R<sub>9</sub> is cladinose (R<sub>12</sub> is CH<sub>3</sub>); and R<sub>11</sub> is CH<sub>3</sub>

10. 6. A compound according to claim 4 wherein R<sub>1</sub> is H; R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>; R<sub>5</sub> is OH; R<sub>6</sub> is CH<sub>3</sub>, R<sub>7</sub> is desosamine; R<sub>8</sub> is CH<sub>3</sub>; R<sub>9</sub> is cladinose (R<sub>12</sub> is CH<sub>3</sub>); and R<sub>11</sub> is CH<sub>3</sub>.

7. A process for making compounds of the formula 1:



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wherein:

R<sub>1</sub> is H or OH; R<sub>2</sub>-R<sub>4</sub> are each independently H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>5</sub> is H or OH; and R<sub>6</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>7</sub> is H or desosamine; R<sub>8</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>; R<sub>9</sub> is OH, mycarose

(R<sub>12</sub> is H), or cladinose (R<sub>12</sub> is CH<sub>3</sub>), R<sub>10</sub> is H; or R<sub>9</sub> = R<sub>10</sub> = O; and R<sub>11</sub> is H, CH<sub>3</sub>, or CH<sub>2</sub>CH<sub>3</sub>

8. A process for making compound of the formula 1 as set out in claim 7 wherein R<sub>1</sub> is OH; R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>; R<sub>5</sub> is OH; R<sub>6</sub> is CH<sub>3</sub>, R<sub>7</sub> is desosamine; R<sub>8</sub> is CH<sub>3</sub>; R<sub>9</sub> is cladinose (R<sub>12</sub> is CH<sub>3</sub>); and R<sub>11</sub> is CH<sub>3</sub>

9. A process for making compound of the formula 1 as set out in claim 7 wherein R<sub>1</sub> is H; R<sub>2</sub>-R<sub>4</sub> are CH<sub>3</sub>; R<sub>5</sub> is OH; R<sub>6</sub> is CH<sub>3</sub>, R<sub>7</sub> is desosamine; R<sub>8</sub> is CH<sub>3</sub>; R<sub>9</sub> is cladinose (R<sub>12</sub> is CH<sub>3</sub>); and R<sub>11</sub> is CH<sub>3</sub>

10. A system for producing a 14-membered macrolide incorporating an acetate starter unit, said system comprising DNA encoding and arranged to express a PKS multienzyme which comprises a loading module and a plurality of extension modules; wherein in the expressed multienzyme, said loading module is adapted to load a malonyl residue and then to effect a decarboxylation of the loaded residue to provide an acetate starter unit which is transferred to an adjacent one of said extension modules; and wherein the extension modules, or at least one thereof, are not naturally associated with a loading module that effects decarboxylation.

11. A system according to claim 10 wherein the macrolide is a compound of formula 1 as defined in any of claims 4-9.

12. A system according to claim 10 or 11 wherein said adjacent extension module to which the acetate starter is transferred is not naturally associated with a loading module that effects decarboxylation.

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13. A system according to claim 10, 11 or 12 wherein the decarboxylating functionality of the loading module is provided by a ketosynthase-type domain having a glutamine residue in the active site.

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14. A system according to claim 10, 11 or 12 wherein the decarboxylating functionality of the loading module is provided by a CLF-type domain.

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15. A system according to claim 14 wherein the CLF-type domain is substantially as any shown in Fig 2.

16. A system according to any of claims 10-15 wherein the loading module's loading functionality is provided by an acyltransferase-type domain having an arginine residue in the active site.

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17. A system according to any of claims 10-16 wherein the loading module includes an acyl carrier protein.

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18. A system according to any of claims 10-13, 16 or 17  
wherein at least the KS<sub>0</sub> domain of said loading module  
corresponds to the loading module of the PKS multienzyme  
of oleandomycin, spiramycin, niddamycin, methymycin, or  
monensin.

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19. A PKS multienzyme as expressible by the DNA of the  
system of any of claims 10-18 or a variant having the  
ability to synthesise a compound of formula 1.

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20. Nucleic acid encoding the PKS multienzyme of  
claim 19.

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21. A vector containing nucleic acid as defined in  
claim 20.

22. A transformant organism comprising a system  
according to any of claims 10-18.

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23. A process according to claim 7, 8, or 9 which  
comprises culturing an organism according to claim 22 and  
recovering a compound of formula 1.

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24. A process according to claim 23 wherein said  
macrolide is a compound of formula 1 as defined in any of  
claims 4-9.

25. A system, organism or process according to any of claims 10-24 wherein the plurality of extension modules corresponds to the extension modules of a PKS selected from erythromycin, narbomycin, pikromycin, lankamycin, kujimycin or megalomycin or a mutant or variant thereof able to direct synthesis of a macrolide.